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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	G0744.70014US02	2693

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EXAMINER	
NOBLE, MARCIA STEPHENS	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/012,904	MEADE ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21,25-27 and 29-35* is/are pending in the application.

4a) Of the above claim(s) *31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Matters

The instant case has been transferred to a new Examiner, Marcia S. Noble.

In view of the Supplemental Appeal Brief filed on 9/10/2008, PROSECUTION IS HEREBY REOPENED. New ground of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632.

Status of Claims

Claims 19, 21, 25-27, 29-35 are pending in the application. Claims 31-35 were previously withdrawn as non-elected subject matter in the Office Actions mailed

8/16/1999 (p. 2) and 4/20/2005 (pp. 9-10). Claims 19, 21, 25-27, 29, and 30 are under consideration.

Withdrawn Rejections

The rejection of claims 19, 21, 25-27, 29 and 30, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, as set forth in the Office Action, mailed 4/20/2005 (pp. 7-8), is withdrawn. Briefly, the specification teaches two separate vectors in Figures 1 and 2 that can be introduced into transgenic mammals. Thus the specification provides written description for "the cell expresses the high and heavy chain separately". Therefore, the new matter rejection is withdrawn.

The rejection of claims 19, 21, 25-27, 29 and 30, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth in the Office Action, mailed 4/20/2005 (pp. 8-9), is withdrawn. This rejection is being withdrawn and replaced with a new 112, 2nd paragraph rejection to clarify the issue of indefiniteness.

The rejection of claims 19 and 25-27, under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97), as set forth in the Office Action, mailed 4/20/2005 (pp. 3-7), is withdrawn. Briefly, Meade et al does not teach an Ig heavy and light chain coding sequence. Therefore, the rejection is withdrawn.

The rejection of claim 21, under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent

No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19 and 25-27 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991), as set forth in the Office Action, mailed 4/20/2005 (p. 7), is withdrawn. Briefly, Meade et al does not teach an Ig heavy and light chain coding sequence. Therefore, the rejection is withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

Two possible construct designs as follows:

A DNA construct for providing a heterologous immunoglobulin (Ig) in the milk of a non-human transgenic mammal comprising a nucleic acid encoding an Ig coding sequence operatively linked to a mammary specific promoter and a 3' non-coding sequence, wherein the construct is produced by inserting the nucleic acid encoding the Ig coding sequence is inserted into a restriction site between the promoter and the 3' non-coding sequence, wherein the Ig coding sequence comprises a nucleic acid

encoding an Ig heavy chain coding region and a nucleic acid encoding an Ig light chain coding region, wherein the expression of the nucleic acids result in the concurrent co-expression of an Ig heavy chain protein and Ig light chain protein, wherein the expression of the nucleic acids results in a individual light chain and an individual heavy chain;

A DNA construct composition for providing a heterologous immunoglobulin (Ig) in the milk of a non-human transgenic mammal, comprising a first nucleic acid encoding an Ig heavy chain operably linked to a mammary specific promoter and a 3' non-coding sequence and a second nucleic acid encoding an Ig light chain operably linked to the mammary specific promoter and a 3' non-coding sequence, wherein the mammary specific promoter of the first and second nucleic acid are the same, and wherein the expression of the nucleic acid results in the co-expression of an independent Ig heavy chain and an independent Ig light chain (see explanation below)

and

A mammary gland epithelial cell comprising the above DNA construct or DNA construct composition, does not reasonably provide enablement for 1) A DNA construct for providing a heterologous Ig in the milk of a non-human mammal that lacks operable linkage between the promoter and the coding sequence for the Ig; and 2) A DNA construct encoding both heavy and light chain Ig genes that comprise two different mammary specific promoters and would not be co-expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

Two different possible construct claims were cited above in the scope of enablement because it is unclear if the claim is intended to comprise one construct with multiple Ig protein coding sequences or if the construct is intended to comprise multiple constructs. This issue is also further discussed in the 112, 2nd paragraph rejection below. Because multiple possibilities for construct design are enabled both options were identified above.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is “undue”.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge

pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claim 19 recites a DNA construct with the intended use of "providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal". Therefore, the DNA construct would require of the elements necessary to promote expression of the heterologous Ig because the intended use for the construct is as an expression construct to produce an Ig protein. The breadth of the claims encompass a construct comprising a coding sequence for an Ig protein that does not have operable linkage to the promoter that results in expression of a protein coding sequence in mammary epithelial cells as claimed.

However, for a transgene to be expressed effectively, it must minimally comprise the elements to be directed by the transcription and translation machinery of the target cell, which requires operable linkage of the protein coding sequence to a promoter capable of driving expression in the target cell (Chen et al US 5,824,837 10/20/1998; see col 2, line 49-53). In the instant case, the specification discloses the use of a goat casein promoter in operable linkage with the coding sequence of heavy and light chain Ig (p. 10, Example 2, line 19 to p. 11, line 26). However, the specification fails to teach a means of expressing an Ig coding sequence that lacks operable linkage to the mammary specific promoter, as encompassed by the claims. Therefore, the breadth of the claims are not enabled because the specification fails to teach a functional DNA construct that can function as an expression vector that lacks operable linkage to the

mammary specific promoter and the art teaches that operable linkage with a promoter is required for successful expression of a transgene, as exemplified by then.

This issue of enablement can be overcome by amending the claims in a manner that teaches operable linkage between the Ig protein-coding sequence and the promoter.

2) The breadth of the claims encompasses a DNA construct or a mammary epithelial cell comprising a DNA construct that encodes for heavy and a light Ig chain genes that are driven by two different promoters and that can be expressed at different times.

The specification teaches multiple milk specific promoters, such as the casein promoters, beta-lactoglobulin promoter, whey acid protein promoter, and the alpha-lactalbumin promoter can be used in the instant invention (p. 6, lines 4-14). The specification further provides working examples that use the goat beta-casein promoter in operably linkage with the Ig light chain gene and Ig heavy chain gene (p. 10, Example, 2, line 26 to p. 11, line 21; Figures 1 and 2).

The specification also teaches that the intended use of the construct is to function as an expression vector to provide heterologous Igs in the milk of a transgenic non-human mammal. The specification further teaches in the transgenic animal, both the light and heavy chain transgenes must be concomitantly co-expressed at the appropriate levels to provide for a structurally functional Ig in the transgenic animal's milk (p. 1, lines 13-14; p. 2, lines 15-18). In the working examples, this is accomplished

by using the same promoter to drive both the light and heavy chain gene expression (Examples 2 and 3, p. 10, line 26 to p. 12, line 5 and Table 1 on p. 12).

However, the art teaches that the different milk specific promoters result in different levels of expression of the gene product depending on the species of animal and the milk specific promoter. For example, the casein art expressed in much greater quantities than alpha-lactalbumin and beta-lactoglobulin (see Milk protein composition printout, p. 2, lane 2 of the SDS-PAGE gel). Therefore, the use of two different milk specific promoters, such as the beta-casein promoter and the alpha-lactalbumin promoter would result in different production of the light and heavy chain gene product. Thus, the use of two different milk specific promoters would not predictably result in a construct that is capable of concomitantly co-expressing the light and heavy chain protein at the appropriate levels, as the specification states is necessary for the function of providing functional Ig to the milk of transgenic mammals.

Therefore, the breadth of the claims that encompass the use of two different milk specific promoters that would result in differential expression of the light and heavy chains is not enabled by the specification because the specification fails to teach a construct that uses two different promoters and that would predictably result in the concomitant expression of the light and heavy chain at the appropriate levels.

This aspect of the enablement rejection may be overcome by amending the claims to specific that the light chain and heavy chain gene use the same promoter and that the construct when expressed result in co-expression of the light and heavy chain Ig proteins.

Therefore at the time of filing the skilled artisan would need to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 21, 25-27, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites, "primarily...of human origin", in line 10. The metes and bound of this recitation is indefinite because it is not apparent how much of the human Ig must be present in the Ig protein to be considered “primarily” of human origin.

Claim 19 recites, "wherein each coding region”, in line 11. This recitation is indefinite because the previous lines of the claims do not recite “coding regions". The previous lines in the claims recite an Ig protein coding sequence. However, it is not apparent that if "each coding region” is referring to the previous recitation of “an immunoglobulin protein coding sequence”. Further, the "an immunoglobulin protein coding sequence” suggests one “coding” sequence, whereas “each coding region” suggests several coding sequences. Therefore, it is not clear if the immunoglobulin protein coding sequence” is meant to comprise “coding regions” or if the “coding regions” are referring to some other sequence.

Claim 19 further recites, "wherein each coding region may be expressed individually". Again, as discussed above, the metes and bounds of this recitation are indefinite because it is unclear how a single Ig protein coding sequence can "be expressed individually".

Claim 19 also recites, "wherein the immunoglobulin protein coding sequence encodes a heavy chain coding region; wherein said immunoglobulin protein coding sequence encodes a light chain coding region", in lines 14-16. This recitation renders the claims indefinite because it is unclear whether the construct encodes both heavy chain and light chain or just one of them. As such, the metes and bounds of the claim cannot be established.

Claims 21, 25-27, 29, and 30 depend upon claim 19.

Claims 29 recites "A mammary epithelial cell comprising the construct of claim 19 and a construct comprising and immunoglobulin protein coding sequence which encodes a both a light and heavy chain operatively linked to a promoter…" This claim is indefinite because it is not clear if the recitation of an additional construct, starting in line 2, is intended to be the same as the construct of claim 19 given they comprise essentially the same elements or if the claims in intended to have additional copies of the same construct.

To overcome these rejections, the claims need to be amended to distinguish if one coding sequence is present or multiple coding sequences are present. Further the claims need to more clearly identify if the construct is intended to have an Ig coding sequence that is different from the heavy and light chain genes, and if this is meant to

be in addition to the coding sequences for the heavy and light chain genes. It is recommended the Applicant refer to the scope of enablement rejection for possible examples to clarify the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 21, 25-27, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surani (WO 90/04036 pub date:4/19/1990), DeBoer (US Patent 5,633,076 effective filing date 11/27/1990; of record), Meade (US 4,873,316 Patent Date: 10/101989; of record), Bischoff (FEBS Letters 305:265-268, 1987; of record), Buhler (Bio/Technology 9:835-838, 1991; of record), Gorden et al (Bio/Technology

5:1183-1187, 1987; of record), Ebert (Bio/Technology 8:140-143, 1990; of record), and Stinnakre (FEBS letters 284:19-22, 1991; of record)

Surani teaches a construct for providing an Ig to serum of a transgenic mouse comprising a nucleic acid encoding a human mu heavy chain and a mouse kappa light chain (Example 1, pp. 7-9; and p. 15, lines 1-8). Surani teaches that such constructs can be modified by means known in the art to target the expression of said nucleic acids encoding the heavy chain and light chain to milk of transgenic animals to allow for harvest of the Ig from milk (p. 2, last par, line 1 to p. 3, line 8). Surani does not explicitly state that "each coding sequence may be expressed individually", as claimed. However, the heavy and light chain are not expressed as a fusion protein, therefore the light and heavy chain of Surani results into two individually expressed proteins. Further, this limitation does not impose a structural limitation, because it is directed to an intended use and therefore these limitations do not carry patentable weight.

Surani does not teach promoter that results in the preferential expression of the Ig coding sequence in mammary epithelial cells and milk, a 3' noncoding sequence, and a unique Xho1 restriction site between the promoter and the non-coding sequence wherein the Ig coding sequence is inserted in the Xho1 restriction site.

However, DeBoer teaches an expression construct for introducing a heterologous protein, most preferably a lactoferin (Lf) protein, into the milk of cows, comprising the bovine alpha s1 casein promoter, a 3' non-coding sequence, a Lf coding sequence inserted into a unique restriction site between the promoter and non-coding sequence, and an Xho1 restriction site between the promoter and the 3'coding

sequence (col 30, lines 40-50 and Figure 7E and Figure 7F). DeBoer teaches that this expression cassette can be used to express a multitude of heterologous polypeptides including Igs (col 7, lines 4-15). DeBoer teaches that the use of this expression construct will allow for a high amount of a heterologous polypeptide expression in the milk (col 8, lines 18-23), thus providing motivation to use this expression construct to produce high quantities of a protein, such as light and heavy Ig chains. DeBoer does not specifically teach the insertion of the coding sequence for a heterologous polypeptide into the Xho1 site between the promoter and non-coding sequence. However, the Xho1 site is between the necessary regulatory elements and the non-coding sequence. Thus ascent evidence to the contrary, it would be within ordinary skill in the art to insert a coding sequence of a heterologous protein into the Xho1 with a reasonable expectation of successful expression of the heterologous protein in the milk of a transgenic mammal. Further, given the finite number of unique restriction sites present between promoter and the non-coding sequence of the expression vector of DeBoer, it would be obvious to an artisan of ordinary skill to choose the Xho1 site with a reasonable expectation of successfully producing a functional expression construct.

Surani does not teach the construct comprising a beta-lactoglobulin promoter, a whey acid protein promoter, or lactalbumin promoter as recited in claim 21.

However, Meade teaches a construct for providing a desired protein in milk of a non-human transgenic mammal comprising a coding sequence for a desired protein to be expressed in milk operatively linked to a milk specific promoter sequence and also encodes a 3' untranslated region (col 1, lines 56-66). Meade further specifies that the

milks specific promoter can be any of the casein promoters, beta-lactoglobulin promoter, or any promoter that targets expression to the mammary tissue (col 1, lines 56-60 and col 3, lines 1-15). Meade teaches that this expression system can be used to express Ig proteins (col 3, lines 31-39). Meade teaches that this expression system also allows for the production of large quantities of the desired protein (col 1, lines 53-55). Bischoff et al. disclose a construct containing a sequence encoding a human α1-antitrypsin variant operatively linked to 17.6 kb of the rabbit whey acid protein promoter, which results in expression and secretion of the a1-antitrypsin variant into milk of a transgenic mouse (see, e.g., page 265, under "DNA construct", page 266, right column, first two paragraphs, and Table 1). Similarly, Gordon et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator (t-PA) operatively linked to the promoter an upstream regulatory sequences from the murine whey acid protein gene, which results in expression and secretion of t-PA into milk of a transgenic mouse (se, e.g., pages 1183-1185, under the sections entitled "Construction of t-PA expression vector", and "Expression of biologically active t-PA in milk). In addition, Ebert et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator operatively linked to the mouse whey acid protein promoter which results in expression of the protein into goat milk (see, e.g., page 835, right column, under "Generation of transgenic goats", page 836, Figure 1, and page 837, left column, under the section entitled "Expression of tPA in milk"). Moreover, Stinnakre et al. disclose a DNA construct comprising a sequence encoding ovine trophoblast interferon operatively linked to the promoter of the ovine α-lactalbumin gene, wherein the

construct is capable of being expressed in the mammary gland of mice and secreted into milk (see, e.g., page 19, right column, under the section entitled “Establishment of the hybrid construct”, page 20, under the section “Expression of the transgene”, and Figure 1, and page 21, Table 1). From the teachings of Bischoff et al., Gordon et al., Ebert et al., and Stinnakre et al., one of ordinary skill in the art would have had a high expectation of successfully producing a protein by the mammary gland which is secreted into the milk of a mammal using a DNA construct which contains a whey acid protein promoter or a lactalbumin promoter, which is known in the art to direct the expression of foreign protein in the mammary gland.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market

forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A-E and G are applicable. At the time of the invention, it would have been obvious to an artisan of ordinary skill to introduce the Ig heavy and light chain coding sequences, taught by Surani, into an expression construct comprising the bovine alpha s1 casein promoter, 3' non-coding sequence, and a unique Xho1 restriction site located between the promoter and non-coding sequence taught by DeBoer using recombinant technologies well established in the art with a reasonable expectation of success. An ordinary artisan would be motivated to introduce the Ig coding sequences of Surani into the expression vector of DeBoer because Surani suggests that these coding sequences can be expressed in the mammary gland to allow for harvest from milk and DeBoer teaches the use of the expression cassette allow for the production of large amounts of a heterologous protein such as Ig proteins. It would have been obvious to an ordinary artisan to choose from a finite number of unique restriction site between the casein promoter and the 3'non-coding sequence to predictably produce an expression construct comprising the Ig coding sequences of Surani inserted into the Xho1 restriction site of the expression construct of DeBoer with a reasonable expectation of arriving at a functional expression vector for introducing heterologous Ig in milk of a transgenic mammal. Further it also would have been obvious to an ordinary artisan to substitute the casein promoter in DeBoer's expression

vector with any one of the equivalent milk specific promoters taught in the art, such as a beta-lactogloblin promoter, as taught by Meade, a whey acid Protein promoter, as taught by Bischoff, Gordon, Ebert, or an alpha-lactabumin promoter, as taught by Stinnakre, to predictably obtain the claimed construct using recombinant technologies well established in the art.

Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Response to Arguments

Applicant's arguments have been fully considered. Some of Applicant's arguments are found persuasive and the rejections of record were withdrawn as such (see above). However, some of Applicant's arguments, particularly pertaining to the art used in the 103 rejections were not found persuasive and these will be addressed.

In the new rejection, Meade is still being used but not as the primary reference. Applicant traverses the teachings of Meade on the grounds that Meade does not teach separate constructs for a light and heavy chain for the production of a single Ig species. Meade also does not teach a unique restriction site that allows for easy modification to insert various Ig chains. Applicant's argument is not found persuasive because Meade is not being provided for these teachings in the new rejection, but rather to demonstrate that other possible equivalent milk specific promoter systems were known in the art and

can reasonably be substituted into the construct. Further it is noted that Meade or any of the other arts used in the new rejection are not required to teach separate constructs for a light and heavy chain because the claims do not require these structural limitations.

In the new rejection, DeBoer is still being used. Applicant traverses the use of DeBoer on the grounds that it does Examiners recitation of col 30, lines 45-50 and Figure 7E do not teach a mammal gland specific promoter and a 3' non-coding sequence, wherein there is a unique restriction site into which Ig coding sequence can be inserted. Applicant's argument is not persuasive. Col 30, lines 45-50 recite "…(FIG. 7E). This plasmid contains 681 bp of bovine alphaS1-casein promoter sequence…the hLF coding region, approximately 1.6 kb of the alphaS1-casein 3' flanking sequence". Therefore, contrary to Applicant's assertion, this recitation teaches construct comprising a milk specific promoter, a coding sequence, and a 3' non-coding sequence. Figure 7E teaches that the Lf coding sequence is flanked by unique restriction site, KpnI and Xho1, wherefore teaching the limitations of unique restrictions sites between the promoter and non-coding sequence. Therefore, DeBoer does teach the limitations of the expression cassette, lacking the Ig coding sequence. However, an artisan of ordinary skill understand that they could use any of these unique restriction sites to insert the Ig codinging sequences into the expression cassette. Thus, DeBoer does teaches the limitations of the expression construct minus the Ig sequence and the art of Surani is used to teach the Ig sequences in the new rejection. Thus, contrary to

Applicant's assertion, DeBoer does teach the limitations of the claims in combination with other prior arts.

Applicant further asserts that DeBoer does not teach or suggest motivation to combine the art. Applicant's argument is not found persuasive because DeBoer teaches that the expression cassette allows for production of a protein of interest, such as Lf, in substantially greater quantities than shown in the previous art (see rejection above for more detail). Thus, DeBoer provides motivation to use their expression cassette for any protein of interest, such as Ig proteins, needed to be expressed in large quantities.

Applicant asserts that an artisan would not have a reasonable expectation of success because the art taught that expression of Ig was unpredictable due to the fact that Ig are multimeric and need specific post translational modifications to be functional Ig. Applicant's arguments are not found persuasive because the claims encompass a product, a DNA construct. The claimed construct has the structural limitations of a milk specific promoter, an Ig coding sequence comprising Ig heavy and light chain coding sequences present in a unique restriction site between the promoter and the non-coding sequence. Claims also encompass a mammary epithelial cell comprising the construct. It is acknowledged that the claims recite such limitations as "may be expressed individually" and "cell expresses the light and heavy chain separately and secretes a heterologous, assembled immunoglobulin light and heavy chain". However, these recitations do not disclose any additional structural limitations. Therefore, the instant case encompasses combining predictable prior art elements with a predictable function

to yield a predictable result. More specifically, the prior art teaches milk specific expression constructs comprising the structural elements of a milk specific promoter, coding sequence in a unique restriction site, and a 3' non-coding sequence that predictable results in the expression of heterologous proteins in the milk. The prior art also teaches Ig heavy and light chains sequences that have been expressed in transgenic mice. Therefore, since the structural elements of the claims have been disclosed in the prior art, demonstrated to predictably function in the prior art, and the claims are not using them in a unique manner that is different from that disclosed in the prior art, an artisan would have a reasonable expectation of successfully producing a construct that results in the same intended Ig product. Therefore, Applicants arguments are not found persuasive.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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